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REVIEW PAPER

Pharmacological potential of *Thymus serpyllum* L. (wild thyme) extracts and essential oil: A review

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Abstract

In traditional medicine *Thymus serpyllum* L. (wild thyme) herb represents a part of a large number of herbal medicinal formulations such as syrups, tinctures, infusions, teas, and decoctions. In recent years, there has been a growing interest in testing the biological properties of wild thyme, because the plant is a high-quality raw material, rich in essential oil and pharmacologically active polyphenolic compounds, which can be included in various formulations in the pharmaceutical, cosmetic, food, and chemical industries. Wild thyme extracts and essential oil have shown significant nitric oxide, ABTS and DPPH radicals scavenging potential, ferrous ion chelating property, reducing activity and ability to inhibit peroxidation of deoxyribonucleic acid (DNA), proteins and lipids. Wild thyme extracts exerted antibacterial activity against *Bacillus cereus*, *Enterococcus faecalis*, *Listeria monocytogenes*, *Staphylococcus aureus*, *Escherichia coli*, *Salmonella enterica*, *Yersinia enterocolitica*, as well as Lactic acid bacteria. Wild thyme essential oil has shown antibacterial potential against *E. coli*, *L. monocytogenes*, *P. aeruginosa*, *S. enteritidis*, *S. aureus*, *Streptococcus salivariu*, *S. mutans, S. sanguinis*, *S. pyogenes*, *E. feacalis*, *B. cereus*, *B. subtilis*, *B. pumilis*, *Lactobacillus acidophilus*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Salmonella choleraesuis*, and *Salmonella poona*. *T. serpyllum* extract possesses antifungal activity against *Fusarium solani*, *F. moniliforme*, *Aspergillus flavus*, *Microsporum canis*, *Alternaria species*, *Candida albicans*, and *C. glabarata*. The essential oil efficiently inhibited the growth of *C. albicans*, *C. glabrata* and *Aspergillus fungi*. Depending on the concentration, wild thyme extract significantly relaxed spontaneous contractions, as well as acetylcholine-, potassium chloride-, barium chloride- and calcium chloride-induced contractions of the isolated rat ileum. The extract significantly reduced the expression of the inducible enzyme cyclooxygenase-2 and inhibited acetylcholinesterase, myeloperoxidase and α-glucosidase activity. *T. serpyllum* extract has shown cytotoxic activity on human breast cancer cell lines, while essential oil has shown the antitumor potential in human cell lung cancer, colon, cervical, hepatocellular, prostate, and breast adeno-carcinoma.

Keywords: pharmacological activity, essential oil, extract, polyphenols, *Thymus serpyllum*

1. INTRODUCTION

The use of aromatic plants and spices was known by ancient Egyptians, Greeks and Romans, due to their flavor, preservative, and medicinal properties (Roby, Sarhan, Selim, & Khalel 2013). Several aromatic plants, including *Thymus serpyllum* L. (wild thyme), generally recognized as safe for their intended use by Food and Drug Administration (FDA), belong to the Lamiaceae family. These plants synthesize and store a large number of various biochemical products which are commercially important and find wide use in food and pharmaceutical industries (Hosseinzadeh, Jafarikukhdan, Hosseini, & Armand 2015). Nowadays, they seem to be "fashionable", because of the health benefits related to their antioxidant, antimicrobial, cytotoxic, antispasmodic, anti-inflammatory, expectorants, and stimulants effects (Boros et al. 2010;

Čančarević, Bugarski, Šavikin, & Zdunić 2013; Nikolić et al. 2014; Rasooli & Mirmostafa 2002; Trifković et al. 2014). These characteristic properties are due to a variety of complex chemical compounds, and hence aromatic plants are generally referred to as "natural bio-chemical factories" or "chemical goldmines". They provide protein, fibre, essential oils, vitamins, minerals, and polyphenolic compounds as one of the major groups which contribute to aromatic plants activities (Costa et al. 2015; A. Jovanović et al. 2019).

In traditional medicine wild thyme herb is a part of a large number of herbal medicinal formulations such as syrups, tinctures, infusions, teas, and decoctions Aziz et al. (2008); Heber (2004); Miron, Plaza, Bahrim, Ibáñez, and Herrero (2011); Nikolić et al. (2014); Stojanovic et al. (2011). Pharmacological documents dating from the 15th century testify to the use of wild thyme in the treatment of headaches caused by colds and laryngitis, as well as in the treatment of diseases of the respiratory, gastrointestinal, and urogenital tract. During the 16th and 17th centuries, *T. serpyllum* was used orally in the treatment of malaria and epilepsy (Adams, Schneider, Kluge, Kessler, & Hamburger 2012). The aerial part of the plant has a long tradition of use as an anthelmintic, antiseptic, diaphoretic, diuretic, analgesic, and expectorant (Aziz et al. 2008). In the Balkan Peninsula, wild thyme is used as a sedative, as an agent for lowering blood cholesterol levels and improving peripheral circulation, and as an immunostimulant (Mustafa et al. 2015). Due to its antispasmodic properties, *T. serpyllum* is used in India for menstrual disorders and pain (Gairola, Sharma, & Bedi 2014). In Chinese medicine, it is used for nausea, diarrhea, flatulence, cough, toothache, itching, and pain (Čančarević et al. 2013). Due to its antimicrobial and antitussive properties, its herb is traditionally used for colds, pharyngitis and coughs (Hussain et al. 2013). *T. serpyllum* herb can be used fresh to make juice, or dry, as part of tea mixture for respiratory diseases (Kovačević 2004). A strong decoction of wild thyme relieves the symptoms of whooping cough and allows the dilution of secretions in bronchitis and asthma, which gives this plant a special place in the treatment of respiratory system diseases (Kayani et al. 2014; Stojanovic et al. 2011). Furthermore, it is used as a stomachic and carminative, because it has the ability to prevent fermentation and gas release, aid digestion and increase the absorption of nutrients (Heber 2004). The use of wild thyme, which has not been proven, but relies on its long-term tradition, is in the treatment of kidney and bladder diseases, dysmenorrhea, and colic (Heber 2004). External application in eczema, wounds and excessive sweating has also been reported, while baths, essential oil and alcoholic extracts have been used in rheumatism, sciatica and sprains (Aziz et al. 2008; Heber 2004; Kozuharova 2013; Mati & de Boer 2011). Due to its pleasant and aromatic taste, as well as antiseptic activity, *T. serpyllum* is used in the manufacture of toothpastes and mouthwashes (Nikolić et al. 2014). Also, a decoction of herb can help prevent hair loss (Aziz et al. 2008). In recent years, there has been a growing interest in testing the medicinal properties of wild thyme, because the plant is a high quality raw material, rich in essential oil and biologically active polyphenolic compounds, which can be included in various formulations in the pharmaceutical, cosmetic, food, and chemical industries. Chemical composition and concentration of pharmacologically active compounds of *T. serpyllum* vary depending on the geographical location, habitat, climatic conditions, stage of plant development, and collection period. The content of wild thyme essential oil varies from 0.1 to 1% (Petrovic et al. 2014). The main component of essential oil is carvacrol, followed by borneol, isobutyl acetate, caryophyllene, 1,8-cineole, citral, citronellal, citronellol, *p*-cymene, geraniol, geranyl acetate, linalool, linalyl acetate, -pinene, γ-terpinene, α-terpineol, terpinyl acetate, and thymol (Heber 2004). Teissedre and Waterhouse (2000) reported that essential oil contains thymol, carvacrol, *p*-cymen, linalol, geraniol, borneol, pinen, and terpinen. According to Hussain et al. (2013), carvacrol, thymol, *o*-cymene, α-terpineol, α-pinene, and β-caryophyllene were the main compounds of wild thyme essential oil (Pakistan). On the other hand, according to Raal, Paaver, Arak, and Orav (2004), geranyl acetate, linalyl acetate, geraniol, and myrcene were the major constituents of *T. serpyllum* essential oil (Estonia). Carvacrol and thymol, isomers present in wild thyme essential oil, belong to the group of monoterpene polyphenols with strong antioxidant and antimicrobial activity (Amorati, Foti, & Valgimigli 2013). In addition to essential oil, wild thyme contains phenolic acids, flavonoids, triterpenes, tannins, and amino acid (Heber 2004; Monographs 2003). According to A. A. Jovanović et al. (2017), ethanol extracts of wild thyme contain 6,8-di-*C*-glucosylapigenin, 6-hydroxyluteolin 7-*O*-glucoside, luteolin 7-*O*-glucuronide, apigenin glucuronide, chlorogenic, caffeic, and rosmarinic acid, as well as salvianolic acid K isomer and salvianolic acid I. In water and ethanol extracts obtained in pressurized liquid extraction, the following compounds were identified: luteolin, luteolin-7-*O*-glucoside, luteolin-7-*O*-glucuronide, eriodictyol-7-*O*-glucuronide, apigenin, apigenin-7-*O*-glucuronide, eriodictyol, caffeic acid ethyl ester, cirsimaritin, prenylnaringenin, syringic, vanillic, chlorogenic, hydroxybenzoic, 4-caffeoylquinic, caffeic, caftaric, and rosmarinic acid (Miron et al. 2011). In methanol extract, some additional compounds were identified: catechin, epicatechin, dihydroquercetin, rutin, quercetin, naringenin, hesperetin, ferulic, and *p*-coumaric acid (Boros et al. 2010; Oszagyán, Simándi, Sawinsky, & Kéry 1996). Oszagyán et al. (1996) reported that chemical composition of wild thyme essential oil and extract obtained by supercritical conditions was approximately the same in qualitative terms, except the amounts of carvacrol, nerol, *p*-cymene, and borneol that were higher in the oil.

This review focuses on the pharmacological potential of *T. serpyllum* extracts and essential oil, discussing their antioxidant, antimicrobial, spasmolytic, enzyme inhibitory, antitumor, and cytotoxic properties.

2. ANTIOXIDANT POTENTIAL OF WILD THYME

Free radicals cause irreversible cellular changes, mainly through the oxidation of lipids, proteins, and nucleic acids, which accelerate the aging process and provoke many diseases, such as cancer, Alzheimer's disease and Parkinson's disease, arthritis, diabetes, and cardiovascular diseases (Mata et al. 2007; Ningappa, Dinesha, & Srinivas 2008; Parejo et al. 2002; Sen & Chakraborty 2011). Kindl, Blažeković, Bucar, and Vladimir-Knežević (2015) reported that ethanol wild thyme extract possessed nitric oxide and DPPH scavenging activity, ferrous ion chelating property, potential reducing activities, ability to inhibit peroxidation of lipids, and high total antioxidant capacities. According to Kulišić, Kriško, Dragović-Uzelac, Miloš, and Pifat (2007), wild thyme infusion reached 91.55% inhibition of DPPH radicals. Mata et al. (2007) reported that both ethanol and water extracts exhibit strong DPPH radical scavenging activity. Oalđe et al. (2020) showed that methanol and ethanol extracts were more active in DPPH radical scavenging assay than butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT). In the same study, the extracts showed genoprotective activity against hydroxyl radicals, with aqueous extracts providing the best DNA protection from free radicals. Rosmarinic acid, as the most abundant compound in wild thyme extract, and luteolin-7-*O*-glucoside (flavone glucoside) are excellent antioxidant and genoprotective agents. Namely, high radical scavenging ability of rosmarinic acid, the major constituent of wild thyme infusion as well, and its relatively rapid kinetic behavior with DPPH radical are responsible for the high level of radical neutralization. Furthermore, other phenolic acids (caffeic acid, *p*-hydroxybenzoic acid) and flavonoids (apigenin, luteolin, quercetin), presented in various *T. serpyllum* extracts (A. A. Jovanović et al. 2017; Komes et al. 2010; Monographs 2003), possess high scavenging ability as well (Kulišić et al. 2007). Hydrolyzed wild thyme extract has shown higher antioxidant capacity in ABTS and FRAP assays compared to non-hydrolyzed sample Komes et al. (2010). Water and ethanol extracts obtained in pressurized liquid extraction have shown antioxidant activity in DPPH and ABTS assays (Miron et al. 2011). However, ethanol extracts obtained using ultrasound probe possessed higher DPPH and ABTS radical scavenging capacity, whereas water extracts represented a weak source of antioxidant agents (Jovanovic et al. 2016). Furthermore, water extracts of wild thyme obtained at high temperature possess better free radical scavenging capacity compared to lavender, mint and sage (Tušek et al. 2018). Moreover, ethanol extracts obtained from wild thyme herbal dust possessed high antioxidant activity determined in ABTS, DPPH and FRAP assays (Mrkonjić et al. 2021). According to Mihailovic-Stanojevic et al. (2013), the ferric reducing/antioxidant power and antioxidant capacity analysis revealed strong antioxidant properties of aqueous extract, as well as *in vitro* nitric oxide-scavenging activity. Wild thyme by-products extract from supercritical fluid extraction significantly reduced lipid and protein oxidation in the ground pork patties (Šojić et al. 2020). Furthermore, in β-Carotene/linoleic acid emulsion the antioxidant activity of water extract was moderate compared to ethanol extract Mata et al. (2007). Lyophilized wild thyme extracts inhibited of β-Carotene oxidation approximately 70-90% depending on the applied extraction procedure (A. Jovanović et al. 2021). Mixture of *T. serpyllum*, *Origanum vulgare*, *Tussilago farfara*, *Valeriana officinalis*, and *Tilia cordata* ethanol extracts inhibited microsomal lipid peroxidation, as well as exhibiting *in vitro* antihemolytic effects (Aralbaeva et al. 2017). Essential oil of *T. serpyllum* showed the highest DPPH radical scavenging activity, reducing power, β-Carotene bleaching inhibition, and TBARS inhibition compared to *T. algeriensis* and *T. vulgaris* essential oils (Nikolić et al. 2014). *T. serpyllum* essential oil possesses strong free radical scavenging activity, due to presence of thymol and carvacrol (Kačániová et al. 2017). Essential oil of wild thyme has shown strong antioxidant capacity in β-Carotene/linoleic acid emulsion due to terpenes Mata et al. (2007). The oxygen-containing fraction of wild thyme essential oil possessed DPPH radical scavenging activity, whereas nonpolar hydrocarbons fraction did not show any radical scavenging effect; thus DPPH radical scavenging effect is determined by the number and substitution pattern of OH groups (Kulisic, Radonic, & Milos 2005). The essential oil showed significantly better ability to neutralize DPPH free radicals compared to synthetic antioxidants BHA and BHT (Petrovic et al. 2014). Essential oil inhibited the copper-catalyzed oxidation of human-low-density lipoproteins (LDL) by 45% depending on total polyphenol content (Kulišić et al. 2007). Furthermore, Teissedre and Waterhouse (2000) reported that the inhibition of oxidation of human low-density lipoproteins (LDL) by polyphenols in wild thyme essential oil was 78-95% depending on the applied concentration.

3. ANTIMICROBIAL POTENTIAL OF WILD THYME

Before modern antibiotics, herbal extracts and essential oils incorporated into pharmaceutical formulations, such as syrups, ointments, and inhalation preparations, were used in the treatment of infective diseases, particularly cough and bronchitis (Fayad, AL-Obaidi, Al-Noor, & Ezzat 2013). The development of synthetic drugs that were both effective against bacterial infections and safe for use, has brought about revolutionary changes in therapy, drastically reducing morbidity and mortality caused by infectious diseases. However, the emergence of the phenomenon of resistance was expected due to the principles of evolution, which determine that all organisms genetically adapt to changes in the environment. This has severely limited the options available for the treatment of many infectious diseases. When phytopreparations are used in the treatment of complex infections, due to the adjuvant and synergistic effect of several different active compounds, the possibility of resistance of microorganisms to antimicrobial agents is reduced (Jovanka et al. 2011; Rang, Dale, Ritter, & Moore 2005). In addition, previous studies have shown that polyphenols can be used in combination with antibiotics to enhance their efficacy and reduce the dose of antibiotics (Singh et al. 2016). In addition to pharmacological applications, antimicrobial agents (mostly synthetic) are widely used in the food industry, in order to prevent the growth of pathogens and microorganisms that cause food spoilage Viuda-Martos et al. (2010). Nowadays, there is a growing interest in the use of natural extracts and essential oils as antimicrobial agents in foods (Al-Fatimi, Wurster, Schröder, & Lindequist 2010; Nikolić et al. 2014; Tepe, Daferera, Sökmen, Polissiou, & Sökmen 2004). Lyophilized *T. serpyllum* extract has shown antibacterial activity against *Bacillus cereus*, *Enterococcus faecalis*, *Listeria monocytogenes*, *Staphylococcus aureus*, *Escherichia coli*, *Salmonella enterica*, and *Yersinia enterocolitica* (A. Jovanović et al. 2021b). Wild thyme by-product extracts obtained in supercritical fluid extraction have shown strong antibacterial potential in meat processing, due to the high content of monoterpene polyphenols which had particularly high antimicrobial properties. Effects of the mentioned extracts on the decrease in the initial total Enterobacteriaceae count could be attributed to major antimicrobial agents, such are carvacrol and thymol. Moreover, compounds present at minor levels, such is phytol, could improve antimicrobial potential of the extracts by synergistic effects. The obtained extracts reduced the growth of Lactic acid bacteria in ground pork patties as well (Šojić et al. 2020). According to Aziz et al. (2008), in methanol wild thyme extract the hexane fraction exhibited significant antifungal activity against *Fusarium solani*, whereas the ethyl acetate fraction has shown strong activity against *Aspergillus flavus*. The chloroform and methanolic fractions showed only moderate antifungal activity against *F. solani* and *Microsporum canis*. Moderate activity of methanol extract was seen against *F. solani*, *F. moniliforme*, *Alternaria species*, *Candida albicans*, and *C. glabarata* (Mannan, Inayatullah, Akhtar, Qayyum, & Mirza 2009). Moreover, lyophilized wild thyme extract has shown growth inhibition of *C. albicans* strains, only in a concentration of 20 mg/mL (A. Jovanović et al. 2021b). *T. serpyllum* essential oil has exhibited significant antibacterial activity against *Streptococcus salivariu*, *S. sanguinis*, *S. pyogenes*, *E. feacalis*, *Bacillus subtilis*, *Lactobacillus acidophilus*, and particularly against *Streptococcus mutans* (Nikolić et al. 2014; Ouedrhiri et al. 2016). Wild thyme essential oil inhibited the growth of Gram-negative bacteria *S. enterica* and *Proteus mirabilis* (Jovanka et al. 2011; Nikolić et al. 2014). However, Gram-negative bacteria are more resistant to the antimicrobial activity of essential oils and extracts, compared to Gram-positive bacteria (Jovanka et al. 2011). Additionally, significant bactericidal activity of essential oil was observed against *Klebsiella pneumoniae* as well (Rasooli & Mirmostafa 2002). Wild thyme essential oils have exhibited antibacterial activity against *Salmonella choleraesuis* and *P. mirabilis* (Jovanka et al. 2011). The essential oil has shown strong antimicrobial activity against *B. cereus*, *B. pumilis*, and *Salmonella poona*, whereas it was active at relatively high concentrations against *Pseudomonas aeruginosa*, *E. coli* and ampicillin-resistant *E. coli* (Hussain et al. 2013). Kačániová et al. (2017) showed significant antimicrobial potential of wild thyme essential oil against *Pseudomonas* spp. Nedorostova, Kloucek, Kokoska, Stolcova, and Pulkrabek (2009) reported the antibacterial activity of *T. serpyllum* essential oil against foodborne bacteria (*L. monocytogenes*, *S. enteritidis*, and *S. aureus*) and showed that essential oil was highly efficient in the vapor phase. Thus, it could be applied against foodborne bacteria in food packaging. (Ouedrhiri et al. 2016) showed synergistic antibacterial effects of essential oil mixtures using *T. serpyllum*, *Origanum compactum* and *O. majorana*. Namely, aromatic compounds, including carvacrol, thymol, *p*-cymene, and γ-terpinene make up most of the chemical composition of wild thyme oil and possess strong antibacterial properties (Amorati et al. 2013; Rasooli & Mirmostafa 2002; **?**). *T. serpyllum* essential oil showed the strongest activity against both fungi and bacteria in comparison to *T. algeriensis* and *T. vulgaris*. Although thymol has been already presented as a good antimicrobial agent, lower thymol and higher terpenes contents were determined in *T. serpyllum* oil then in other *Thymus* species (Nikolić et al. 2014; Pioro-Jabrucka, Suchorska-Tropilo, & Rzewuska 2007). Thus, thymol is not the only one responsible for the achieved antimicrobial activity.

The oil efficiently inhibited the growth of *Candida* spp.; *C. tropicalis*, *C. krusei*, and *C. glabrata* proved to be involved in the disease course, and together with *C. albicans* represent more than 80% of human cavity clinical isolates (Nikolić et al. 2014). Pavel and Alecu (2008) reported that essential oil possessed antifungal activity against *C. albicans* isolates recovered from a patient with clinical signs of oral candidosis and from healthy carriers, as well as against *C. glabrata* recovered from a patient with oral candidosis associated to denture and diabetes. Essential oil inhibited fungal growth and ochratoxin A biosynthesis in *Aspergillus* fungi growing on stored food as well (Sokolić-Mihalak et al. 2012).

4. SPASMOLYTIC POTENTIAL OF WILD THYME

Spasmolytics are natural or synthetic components that cause relaxation of the smooth muscles of the respiratory, gastrointestinal, biliary, and urogenital tract, either directly or by inhibiting the parasympathetic nervous system (Rang et al. 2005). Flavonoids affect cholinergic M_3 and histamine H_1 receptors, which leads to a reduction in histamine-induced contractions in bronchial asthma (Melzig, Pertz, & Krenn 2001). Similar to flavonoids, coumarins relax the smooth muscles of the cardiovascular system by inhibiting the mobilization of intracellular Ca^{2+} ions, located in noradrenaline-sensitive structures (Dussossoy et al. 2016). Compounds present in plant species of the Lamiaceae family (flavones and glycoside flavones) exhibit a spasmolytic effect by activating nicotinic receptors, prostaglandins and Ca^{2+} channels, and inhibit contractions caused by acetylcholine, histamine and barium ions (Brankovic et al. 2011). Thymol and carvacrol also have the ability to relax smooth muscles (Engelbertz, Lechtenberg, Studt, Hensel, & Verspohl 2012). Quercetin, quercetin glycosides and tannins show spasmolytic activity by the mechanism of inhibition of acetylcholine- and potassium ions-induced contractions (Tona et al. 2000). Depending on the concentration, wild thyme extract significantly relaxed spontaneous contractions, as well as acetylcholine-, potassium chloride-, barium chloride- and calcium chloride-induced contractions of the isolated rat ileum. The extract obtained in maceration has also shown a dose-dependent spasmolytic effect in the model of barium chloride- and calcium chloride-induced contractions (A. Jovanović et al. 2021). Considering the fact that wild thyme extracts have shown a significant influence on relaxation of smooth muscles in the presence of acetylcholine, high concentrations of potassium or calcium ions, it can be concluded that the antispasmodic activity is achieved by Ca^{2+} channel blockade and by prevention of the Ca^{2+} ions influx from extracellular medium. Furthermore, wild thyme extract reduced barium ions-induced contraction by inhibiting K^+ channels. Namely, polyphenols, including apigenin, luteolin, thymol, and carvacrol (present in *T. serpyllum*) exhibited spasmolytic activity on smooth muscle via Ca^{2+} channel blockade and anticholinergic effect (A. Jovanović et al. 2021).

5. ENZYME INHIBITION POTENTIAL OF WILD THYME

Polyphenols can inhibit various enzymes, such as acetylcholinesterase, which causes hydrolysis of neurotransmitters and thus inhibits signal transfer at synapses; butyrylcholinesterase, a hydrolyzing enzyme of blood plasma; xanthine oxidases involved in the metabolism of purines and uric acid; monoamine oxidase, which participates in the inactivation of neurotransmitters, etc. (Ertas et al. 2015; Lee et al. 2011; Mata et al. 2007). These phytochemicals can inhibit angiotensin-converting enzyme (ACE) activity as well, and thus affect hypertension and diseases of the cardiovascular system caused by excessive production of angiotensin II (Juturu 2014). Wild thyme extract significantly reduced the expression of the inducible enzyme cyclooxygenase-2 (COX-2) that had a key role in the inflammatory response in colitic rats. Moreover, the extract has caused a significant reduction in colonic myeloperoxidase activity, thus preventing the massive neutrophil infiltration into the inflamed tissue, i.e. colonic damage in colitis (Algieri et al. 2014). The extract has shown acetylcholinesterase (AChE) inhibitory activity in a dose-dependent manner (Kindl et al. 2015). According to Mata et al. (2007), inhibition capacity of *T. serpyllum* against AChE showed the following order: essential oil>ethanol extract>water extract; carvacrol was recognized as the major compound of essential oil, possessing strong inhibitory activity. The mentioned results highlighted *T. serpyllum* extract as a rich source of natural antioxidants and AChE inhibitors that could be useful in preventing and treating of neurodegenerative disorders, such as Alzheimer's disease. Methanolic and aqueous extracts showed more than 50% inhibitory effect on the α-glucosidase. Namely, glucosidase inhibitors from plants might be the new, reliable, cheap, and safe drug in the control of diabetes, lysosomal storage diseases, human immunodeficiency virus infection, and metastatic cancer (Gholamhoseinian, Fallah, Sharifi-far, & Mirtajaddini 2008). According to Alamgeer (2012), the aqueous extract of *T. serpyllum* significantly increased the blood glucose level in diabetic rabbits, thus it can be concluded that the hypoglycemic effect might be due to the α-glucosidase inhibition.

6. ANTITUMOR AND CYTOTOXIC POTENTIAL OF WILD THYME

Several studies have reported antitumor potential of polyphenols and proposed multiple mechanisms leading to inhibition of tumor growth (Berdowska et al. 2013; Fresco, Borges, Marques, & Diniz 2010; Galati & O'Brien 2004; Neergheen, Bahorun, Taylor, Jen, & Aruoma 2010). Polyphenols can reduce tumor growth *via* the induction of apoptosis, arrest of tumor cells in specific phases, induction of detoxifying and antioxidant enzyme systems, inhibition of signaling pathways inducing cellular proliferation or increasing the protection against carcinogenic factors (Berdowska et al. 2013; Fresco et al. 2010; Neergheen et al. 2010). Moreover, some polyphenol compounds can downregulate the enzymes involved in the prostaglandins synthesis (such is COX-2) that can promote carcinogenesis, and exhibit antiangiogenic properties resulting in the restriction of the growth and development of solid tumors (Algieri et al. 2014; Berdowska et al. 2013). In two studies, aqueous and methanol wild thyme extracts have achieved cytotoxic activity on human breast cancer cell lines, with induction of apoptosis and inhibition of DNA methyltransferase and histone deacetylase, enzymes that caused changes in the DNA molecule and chromosomes (Berdowska et al. 2013; Bozkurt et al. 2012). Namely, according to Berdowska et al. (2013), dried *T. serpyllum* aqueous extract exhibited the increase of the viability of the wild-type MCF-7 human breast cancer cells, and decrease in the viability of adriamycin-resistant MCF-7/Adr cancer cells, at relatively high doses. The extract induced significant cytotoxicity in breast cancer cells in a time- and dose-dependent manner, without the influence on normal cells, even at the highest concentrations. It induced apoptosis and inhibited the DNA methyltransferase and histone deacetylase activities in cancer cells, which was associated with a decrease in messenger ribonucleic acid (mRNA) expression Bozkurt et al. (2012). Mixture of *T. serpyllum*, *O. vulgare*, *T. farfara*, *V.officinalis*, and *T. cordata* ethanol extracts effectively activated the nuclear factor erythroid 2-related factor 2/antioxidant response element (Nrf2/ARE), i.e. the cytoprotective transcriptional system, in HepG2 hepatocarcinoma human cells (Aralbaeva et al. 2017). *T. serpyllum* essential oil was the most potent in human tumor cell lines, including non-small cell lung cancer, colon, cervical, hepatocellular, and breast adeno-carcinoma compared to *T. algeriensis* and *T. vulgaris* Nikolić et al. (2014). Carvacrol and thymol (as major constituents of essential oil) possess *in vitro* cytotoxic activity against tumor cells and may be involved in the stimulation of active proliferation of pulp fibroblasts (M'Barek et al. 2007; Nikolić et al. 2014). Essential oil has the ability to inhibit the proliferation of fibroblast cells and hormone-dependent prostate cancer as well (Hussain et al. 2013).

7. CONCLUSION

Use of wild thyme based on the human experience and long-standing tradition includes the treatment of respiratory, gastrointestinal, and urogenital tract diseases, as well as in eczema, wounds, excessive sweating, rheumatism, sciatica, and sprains. This review paper provides information about antioxidant, antimicrobial, spasmolytic, enzyme inhibitory, antitumor, and cytotoxic potential of *T. serpyllum* extracts and essential oil. Due to the pharmacological properties presented in this review article, *T. serpyllum*extracts and essential oil represent an important natural resource for the pharmaceutical industry. Namely, due to antioxidant, antimicrobial and antispasmodic activities, wild thyme extract may be used as adjuvant in therapy of gastrointestinal disorders and infections.

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CONFLICT OF INTEREST

The authors declare that they have no financial and commercial conflicts of interest.

REFERENCES

Adams, M., Schneider, S.-V., Kluge, M., Kessler, M., & Hamburger, M. (2012). Epilepsy in the renaissance: A survey of remedies from 16th and 17th century german herbals. *Journal of Ethnopharmacology*, *143*(1), 1–13. https://doi.org/10.1016/j.jep.2012.06.010

Alamgeer, A. (2012). Hypoglycemic and hematological effects of aqueous extract of thymus serpyllum linn. in alloxan-induced diabetic rabbits. *African Journal of Pharmacy and Pharmacology*, *6*(40), 2845–2850. https://doi.org/10.5897/ajpp12.1343

Al-Fatimi, M., Wurster, M., Schröder, G., & Lindequist, U. (2010). In vitro antimicrobial, cytotoxic and radical scavenging activities and chemical constituents of the endemic thymus laevigatus (vahl). *Records of Natural Products*, *4*(1), 49.

Algieri, F., Rodriguez-Nogales, A., Garrido-Mesa, N., Zorrilla, P., Burkard, N., Pischel, I., … Galvez, J. (2014). Intestinal anti-inflammatory activity of the serpylli herba extract in experimental models of rodent colitis. *Journal of Crohn's and Colitis*, *8*(8), 775–788. https://doi.org/10.1016/j.crohns.2013.12.012

Amorati, R., Foti, M. C., & Valgimigli, L. (2013). Antioxidant activity of essential oils. *Journal of Agricultural and Food Chemistry*, *61*(46), 10835–10847. https://doi.org/10.1021/jf403496k

Aralbaeva, A. N., Mamataeva, A. T., Zhaparkulova, N. I., Utegalieva, R. S., Khanin, M., Danilenko, M., & Murzakhmetova, M. K. (2017). A composition of medicinal plants with an enhanced ability to suppress microsomal lipid peroxidation and a protective activity against carbon tetrachloride-induced hepatotoxicity. *Biomedicine &amp Pharmacotherapy*, *96*, 1283–1291. https://doi.org/10.1016/j.biopha.2017.11.085

Aziz, S., et al. (2008). Studies on the chemical constituents of thymus serpyllum. *Turkish Journal of Chemistry*, *32*(5), 605–614.

Berdowska, I., Zieliński, B., Fecka, I., Kulbacka, J., Saczko, J., & Gamian, A. (2013). Cytotoxic impact of phenolics from lamiaceae species on human breast cancer cells. *Food Chemistry*, *141*(2), 1313–1321. https://doi.org/10.1016/j.foodchem.2013.03.090 doi: 10.1016/j.foodchem.2013.03.090

Boros, B., Jakabová, S., Dörnyei, Á., Horváth, G., Pluhár, Z., Kilár, F., & Felinger, A. (2010). Determination of polyphenolic compounds by liquid chromatography–mass spectrometry in thymus species. *Journal of Chromatography A*, *1217*(51), 7972–7980. https://doi.org/10.1016/j.chroma.2010.07.042

Bozkurt, E., Atmaca, H., Kisim, A., Uzunoglu, S., Uslu, R., & Karaca, B. (2012). Effects ofithymus serpyllum/iextract on cell proliferation, apoptosis and epigenetic events in human breast cancer cells. *Nutrition and Cancer*, *64*(8), 1245–1250. https://doi.org/10.1080/01635581.2012.719658

Brankovic, S., Kitic, D., Radenkovic, M., Veljkovic, S., Jankovic, T., Savikin, K., & Zdunic, G. (2011). Spasmolytic activity of the ethanol extract of isideritis raeseri/i spp. iraeseri/i boiss. &amp heldr. on the isolated rat ileum contractions. *Journal of Medicinal Food*, *14*(5), 495–498. https://doi.org/10.1089/jmf.2010.0036

Čančarević, A., Bugarski, B., Šavikin, K., & Zdunić, G. (2013). Biological activity and ethnomedicinal use of thymus vulgaris and thymus serpyllum. *Lekovite sirovine*(33), 3–17.

Costa, D. C., Costa, H., Albuquerque, T. G., Ramos, F., Castilho, M., & Sanches-Silva, A. (2015). Advances in phenolic compounds analysis of aromatic plants and their potential applications. *Trends in Food Science &amp Technology*, *45*(2), 336–354. https://doi.org/10.1016/j.tifs.2015.06.009

Dussossoy, E., Bichon, F., Bony, E., Portet, K., Brat, P., Vaillant, F., … Poucheret, P. (2016). Pulmonary anti-inflammatory effects and spasmolytic properties of costa rican noni juice (morinda citrifolia l.). *Journal of Ethnopharmacology*, *192*, 264–272. https://doi.org/10.1016/j.jep.2016.07.038

Engelbertz, J., Lechtenberg, M., Studt, L., Hensel, A., & Verspohl, E. J. (2012). Bioassay-guided fractionation of a thymol-deprived hydrophilic thyme extract and its antispasmodic effect. *Journal of Ethnopharmacology*, *141*(3), 848–853. https://doi.org/10.1016/j.jep.2012.03.025

Ertas, A., Boga, M., Yilmaz, M. A., Yesil, Y., Tel, G., Temel, H., … Ugurlu, P. (2015). A detailed study on the chemical and biological profiles of essential oil and methanol extract of thymus nummularius (anzer tea): Rosmarinic acid. *Industrial Crops and Products*, *67*, 336–345. https://doi.org/10.1016/j.indcrop.2015.01.064

Fayad, N., AL-Obaidi, O. H. S., Al-Noor, T. H., & Ezzat, M. O. (2013). Water and alcohol extraction of thyme plant (thymus vulgaris) and activity study against bacteria, tumors and used as anti-oxidant in margarine manufacture. *Innovative Systems Design and Engineering*, *4*(1), 41–51.

Fresco, P., Borges, F., Marques, M., & Diniz, C. (2010). The anticancer properties of dietary polyphenols and its relation with apoptosis. *Current Pharmaceutical Design*, *16*(1), 114–134. https://doi.org/10.2174/138161210789941856

Gairola, S., Sharma, J., & Bedi, Y. S. (2014). A cross-cultural analysis of jammu, kashmir and ladakh (india) medicinal plant use. *Journal of Ethnopharmacology*, *155*(2), 925–986. https://doi.org/10.1016/j.jep.2014.06.029

Galati, G., & O'Brien, P. J. (2004). Potential toxicity of flavonoids and other dietary phenolics: significance for their chemopreventive and anticancer properties. *Free Radical Biology and Medicine*, *37*(3), 287–303. https://doi.org/10.1016/j.freeradbiomed.2004.04.034

Gholamhoseinian, A., Fallah, H., Sharifi-far, F., & Mirtajaddini, M. (2008). The inhibitory effect of some iranian plants extracts on the alpha glucosidase. *Iranian Journal of Basic Medical Sciences*, *11*(1). https://doi.org/10.22038/ijbms.2008.5190

Heber, D. (2004). *Pdr for herbal medicines*. Thomson PDR.

Hosseinzadeh, S., Jafarikukhdan, A., Hosseini, A., & Armand, R. (2015). The application of medicinal plants in traditional and modern medicine: A review of &amplti&ampgtthymus vulgaris&amplt/i&ampgt. *International Journal of Clinical Medicine*, *06*(09), 635–642. https://doi.org/10.4236/ijcm.2015.69084

Hussain, A. I., Anwar, F., Chatha, S. A., Latif, S., Sherazi, S. T., Ahmad, A., … Sarker, S. D. (2013). Chemical composition and bioactivity studies of the essential oils from two thymus species from the pakistani flora. *LWT - Food Science and Technology*, *50*(1), 185–192. https://doi.org/10.1016/j.lwt.2012.06.003

Jovanka, L., Ivana, C., Goran, T., Sava, P., Slavica, S., Tamara, C.-G., & Ljiljana, K. (2011). In vitro antibacterial activity of essential oils from plant family lamiaceae. *Rom Biotech Lett*, *16*(2), 6034–6041.

Jovanović, A., Djordjević, V., Petrović, P., Pljevljakušić, D., Zdunić, G., Šavikin, K., & Bugarski, B. (2021b). The influence of different extraction conditions on polyphenol content, antioxidant and antimicrobial activities of wild thyme. *Journal of Applied Research on Medicinal and Aromatic Plants*, *25*, 100328. https://doi.org/10.1016/j.jarmap.2021.100328

Jovanovic, A., Djordjevic, V., Zdunic, G., Savikin, K., Pljevljakusic, D., & Bugarski, B. (2016). Ultrasound-assisted extraction of polyphenols from thymus serpyllum and its antioxidant activity. *Chemical Industry*, *70*(4), 391–398. https://doi.org/10.2298/hemind150629044j

Jovanović, A., Petrović, P., Zdunić, G., Šavikin, K., Kitić, D., Đorđević, V., … Branković, S. (2021). Influence of lyophilized thymus serpyllum l. extracts on the gastrointestinal system: Spasmolytic, antimicrobial and antioxidant properties. *South African Journal of Botany*, *142*, 274–283. https://doi.org/10.1016/j.sajb.2021.06.028

Jovanović, A., Skrt, M., Petrović, P., Častvan, I., Zdunić, G., Šavikin, K., & Bugarski, B. (2019). Ethanol thymus serpyllum extracts: Evaluation of extraction conditions via total polyphenol content and radical scavenging activity. *Lekovite sirovine*(39), 23–29. https://doi.org/10.5937/leksir1939023j

Jovanović, A. A., Đorđević, V. B., Zdunić, G. M., Pljevljakušić, D. S., Šavikin, K. P., Gođevac, D. M., & Bugarski, B. M. (2017). Optimization of the extraction process of polyphenols from thymus serpyllum l. herb using maceration, heat- and ultrasound-assisted techniques. *Separation and Purification Technology*, *179*, 369–380. https://doi.org/10.1016/j.seppur.2017.01.055

Juturu, V. (2014). Polyphenols and cardiometabolic syndrome. In *Polyphenols in human health and disease* (pp. 1067–1076). Elsevier. https://doi.org/10.1016/b978-0-12-398456-2.00082-7

Kačániová, M., Terentjeva, M., Vukovic, N., Puchalski, C., Roychoudhury, S., Kunová, S., … Ivanišová, E. (2017). The antioxidant and antimicrobial activity of essential oils against pseudomonas spp. isolated from fish. *Saudi Pharmaceutical Journal*, *25*(8), 1108–1116. https://doi.org/10.1016/j.jsps.2017.07.005

Kayani, S., Ahmad, M., Zafar, M., Sultana, S., Khan, M. P. Z., Ashraf, M. A., … Yaseen, G. (2014). Ethnobotanical uses of medicinal plants for respiratory disorders among the inhabitants of gallies – abbottabad, northern pakistan. *Journal of Ethnopharmacology*, *156*, 47–60. https://doi.org/10.1016/j.jep.2014.08.005

Kindl, M., Blažeković, B., Bucar, F., & Vladimir-Knežević, S. (2015). Antioxidant and anticholinesterase potential of sixithymus/ispecies. *Evidence-Based Complementary and Alternative Medicine*, *2015*, 1–10. https://doi.org/10.1155/2015/403950

Komes, D., Belščak-Cvitanović, A., Horžić, D., Rusak, G., Likić, S., & Berendika, M. (2010). Phenolic composition and antioxidant properties of some traditionally used medicinal plants affected by the extraction time and hydrolysis. *Phytochemical Analysis*, *22*(2), 172–180. https://doi.org/10.1002/pca.1264

Kovačević, N. (2004). *Osnovi farmakognozije*. Srpska školska knjiga.

Kozuharova, E. (2013). Descriptive study of contemporary status of the traditional knowledge on medicinal plants in bulgaria. *African Journal of Pharmacy and Pharmacology*, *7*(5), 185–198. https://doi.org/10.5897/ajpp12.871

Kulišić, T., Kriško, A., Dragović-Uzelac, V., Miloš, M., & Pifat, G. (2007). The effects of essential oils and aqueous tea infusions of oregano (ioriganum vulgare/il. spp.ihirtum/i), thyme (ithymus vulgaris/il.) and wild thyme (ithymus serpyllum/il.) on the copper-induced oxidation of human low-density lipoproteins. *International Journal of Food Sciences and Nutrition*, *58*(2), 87–93. https://doi.org/10.1080/09637480601108307

Kulisic, T., Radonic, A., & Milos, M. (2005). Antioxidant properties of thyme (thymus vulgaris l.) and wild thyme (thymus serpyllum l.) essential oils. *Italian journal of food science*, *17*(3), 315.

Lee, C.-J., Chen, L.-G., Chang, T.-L., Ke, W.-M., Lo, Y.-F., & Wang, C.-C. (2011). The correlation between skin-care effects and phytochemical contents in lamiaceae plants. *Food Chemistry*, *124*(3), 833–841. https://doi.org/10.1016/j.foodchem.2010.07.003

Mannan, A., Inayatullah, S., Akhtar, M. Z., Qayyum, M., & Mirza, B. (2009). Biological evaluation of wild thyme (ithymus serpyllum/i). *Pharmaceutical Biology*, *47*(7), 628–633. https://doi.org/10.1080/13880200902915622

Mata, A., Proença, C., Ferreira, A., Serralheiro, M., Nogueira, J., & Araújo, M. (2007). Antioxidant and antiacetylcholinesterase activities of five plants used as portuguese food spices. *Food Chemistry*, *103*(3), 778–786. https://doi.org/10.1016/j.foodchem.2006.09.017

Mati, E., & de Boer, H. (2011). Ethnobotany and trade of medicinal plants in the qaysari market, kurdish autonomous region, iraq. *Journal of Ethnopharmacology*, *133*(2), 490–510. https://doi.org/10.1016/j.jep.2010.10.023

M'Barek, L. A., Mouse, H. A., Jaâfari, A., Aboufatima, R., Benharref, A., Kamal, M., … Zyad, A. (2007). Cytotoxic effect of essential oil of thyme (thymus broussonettii) on the IGR-OV1 tumor cells resistant to chemotherapy. *Brazilian Journal of Medical and Biological Research*, *40*(11), 1537–1544. https://doi.org/10.1590/s0100-879x2007001100014

Melzig, M., Pertz, H., & Krenn, L. (2001). Anti-inflammatory and spasmolytic activity of extracts from droserae herba. *Phytomedicine*, *8*(3), 225–229. https://doi.org/10.1078/0944-7113-00031

Mihailovic-Stanojevic, N., Belščak-Cvitanović, A., Grujić-Milanović, J., Ivanov, M., Jovović, D., Bugarski, D., & Miloradović, Z. (2013). Antioxidant and antihypertensive activity of extract from thymus serpyllum l. in experimental hypertension. *Plant Foods for Human Nutrition*, *68*(3), 235–240. https://doi.org/10.1007/s11130-013-0368-7

Miron, T., Plaza, M., Bahrim, G., Ibáñez, E., & Herrero, M. (2011). Chemical composition of bioactive pressurized extracts of romanian aromatic plants. *Journal of Chromatography A*, *1218*(30), 4918–4927. https://doi.org/10.1016/j.chroma.2010.11.055

Monographs, E. (2003). *European scientific cooperative on phytotherapy.*

Mrkonjić, Ž., Rakić, D., Olgun, E. O., Canli, O., Kaplan, M., Teslić, N., … Pavlić, B. (2021). Optimization of antioxidants recovery from wild thyme (thymus serpyllum l.) by ultrasound-assisted extraction: Multi-response approach. *Journal of Applied Research on Medicinal and Aromatic Plants*, *24*, 100333. https://doi.org/10.1016/j.jarmap.2021.100333

Mustafa, B., Hajdari, A., Pieroni, A., Pulaj, B., Koro, X., & Quave, C. L. (2015). A cross-cultural comparison of folk plant uses among albanians, bosniaks, gorani and turks living in south kosovo. *Journal of Ethnobiology and Ethnomedicine*, *11*(1). https://doi.org/10.1186/s13002-015-0023-5

Nedorostova, L., Kloucek, P., Kokoska, L., Stolcova, M., & Pulkrabek, J. (2009). Antimicrobial properties of selected essential oils in vapour phase against foodborne bacteria. *Food Control*, *20*(2), 157–160. https://doi.org/10.1016/j.foodcont.2008.03.007

Neergheen, V. S., Bahorun, T., Taylor, E. W., Jen, L.-S., & Aruoma, O. I. (2010). Targeting specific cell signaling transduction pathways by dietary and medicinal phytochemicals in cancer chemoprevention. *Toxicology*, *278*(2), 229–241. https://doi.org/10.1016/j.tox.2009.10.010

Nikolić, M., Glamočlija, J., Ferreira, I. C., Calhelha, R. C., Fernandes, Â., Marković, T., … Soković, M. (2014). Chemical composition, antimicrobial, antioxidant and antitumor activity of thymus serpyllum l., thymus algeriensis boiss. and reut and thymus vulgaris l. essential oils. *Industrial Crops and Products*, *52*, 183–190. https://doi.org/10.1016/j.indcrop.2013.10.006

Ningappa, M. B., Dinesha, R., & Srinivas, L. (2008). Antioxidant and free radical scavenging activities of polyphenol-enriched curry leaf (murraya koenigii l.) extracts. *Food Chemistry*, *106*(2), 720–728. https://doi.org/10.1016/j.foodchem.2007.06.057

Oalđe, M. M., Kolarević, S. M., Živković, J. C., Vuković-Gačić, B. S., Marić, J. M. J., Kolarević, M. J. K., … Duletić-Laušević, S. N. (2020). The impact of different extracts of six lamiaceae species on deleterious effects of oxidative stress assessed in acellular, prokaryotic and eukaryotic models in vitro. *Saudi Pharmaceutical Journal*, *28*(12), 1592–1604. https://doi.org/10.1016/j.jsps.2020.10.006

Oszagyán, M., Simándi, B., Sawinsky, J., & Kéry, Á. (1996). A comparison between the oil and supercritical carbon dioxide extract of hungarian wild thymei(thymus serpyllum/il.). *Journal of Essential Oil Research*, *8*(3), 333–335. https://doi.org/10.1080/10412905.1996.9700629

Ouedrhiri, W., Balouiri, M., Bouhdid, S., Moja, S., Chahdi, F. O., Taleb, M., & Greche, H. (2016). Mixture design of origanum compactum, origanum majorana and thymus serpyllum essential oils: Optimization of their antibacterial effect. *Industrial Crops and Products*, *89*, 1–9. https://doi.org/10.1016/j.indcrop.2016.04.049

Parejo, I., Viladomat, F., Bastida, J., Rosas-Romero, A., Flerlage, N., Burillo, J., & Codina, C. (2002). Comparison between the radical scavenging activity and antioxidant activity of six distilled and nondistilled mediterranean herbs and aromatic plants. *Journal of Agricultural and Food Chemistry*, *50*(23), 6882–6890. https://doi.org/10.1021/jf020540a

Pavel, M., & Alecu, F. (2008). Antifungal activity of thymus serpyllum essential oil against candida albicans and candida non-albicans clinical isolates. In *18th european congress of clinical microbiology and infectious diseases (eccmid.* Bucharest, Romania: PDR for Herbal Medicines.

Petrovic, S., Ristic, M., Petrovic, N., Lazic, M., Franciskovic, M., & Petrovic, S. (2014). Chemical composition and antioxidative activity of essential oil of thymus serpyllum l. *Chemical Industry*, *68*(3), 389–397. https://doi.org/10.2298/hemind130513051p

Pioro-Jabrucka, E., Suchorska-Tropilo, K., & Rzewuska, M. (2007). Antibacterial activity of the essential oil of common thyme [thymus pulegioides l.] and wild thyme [thymus serpyllum l.]. *Herba Polonica*, *3*(53).

Raal, A., Paaver, U., Arak, E., & Orav, A. (2004). Content and composition of the essential oil of thymus serpyllum l. growing wild in estonia. *Medicina (Kaunas)*, *40*(8), 795–800.

Rang, H., Dale, M., Ritter, J., & Moore, P. (2005). *Farmakologija*. Belgrade, Serbia: Data status.

Rasooli, I., & Mirmostafa, S. A. (2002). Antibacterial properties of thymus pubescens and thymus serpyllum essential oils. *Fitoterapia*, *73*(3), 244–250. https://doi.org/10.1016/s0367-326x(02)00064-3

Roby, M. H. H., Sarhan, M. A., Selim, K. A.-H., & Khalel, K. I. (2013). Evaluation of antioxidant activity, total phenols and phenolic compounds in thyme (thymus vulgaris l.), sage (salvia officinalis l.), and marjoram (origanum majorana l.) extracts. *Industrial Crops and Products*, *43*, 827–831. https://doi.org/10.1016/j.indcrop.2012.08.029

Sen, S., & Chakraborty, R. (2011). The role of antioxidants in human health. In *ACS symposium series* (pp. 1–37). American Chemical Society. https://doi.org/10.1021/bk-2011-1083.ch001

Singh, J. P., Kaur, A., Singh, N., Nim, L., Shevkani, K., Kaur, H., & Arora, D. S. (2016). In vitro antioxidant and antimicrobial properties of jambolan (syzygium cumini) fruit polyphenols. *LWT - Food Science and Technology*, *65*, 1025–1030. https://doi.org/10.1016/j.lwt.2015.09.038

Šojić, B., Tomović, V., Kocić-Tanackov, S., Kovačević, D. B., Putnik, P., Mrkonjić, Ž., … Pavlić, B. (2020). Supercritical extracts of wild thyme (thymus serpyllum l.) by-product as natural antioxidants in ground pork patties. *LWT*, *130*, 109661. https://doi.org/10.1016/j.lwt.2020.109661

Sokolić-Mihalak, D., Frece, J., Slavica, A., Delaš, F., Pavlović, H., & Markov, K. (2012). The effects of wild thyme (thymus serpyllum l.) essential oil components against ochratoxin-producing aspergilli / majčina dušica (thymus serpyllum l.) i njezine komponente protiv okratoksikotvornih vrsta aspergillusa. *Archives of Industrial Hygiene and Toxicology*, *63*(4), 457–462. https://doi.org/10.2478/10004-1254-63-2012-2309

Stojanovic, R., Belscak-Cvitanovic, A., Manojlovic, V., Komes, D., Nedovic, V., & Bugarski, B. (2011). Encapsulation of thyme (thymus serpyllum l.) aqueous extract in calcium alginate beads. *Journal of the Science of Food and Agriculture*, *92*(3), 685–696. https://doi.org/10.1002/jsfa.4632

Teissedre, P. L., & Waterhouse, A. L. (2000). Inhibition of oxidation of human low-density lipoproteins by phenolic substances in different essential oils varieties. *Journal of Agricultural and Food Chemistry*, *48*(9), 3801–3805. https://doi.org/10.1021/jf990921x

Tepe, B., Daferera, D., Sökmen, M., Polissiou, M., & Sökmen, A. (2004). In vitro antimicrobial and antioxidant activities of the essential oils and various extracts of ithymus eigii/i m. zohary et p.h. davis. *Journal of Agricultural and Food Chemistry*, *52*(5), 1132–1137. https://doi.org/10.1021/jf035094l

Tona, L., Kambu, K., Ngimbi, N., Mesia, K., Penge, O., Lusakibanza, M., … Vlietinck, A. (2000). Antiamoebic and spasmolytic activities of extracts from some antidiarrhoeal traditional preparations used in kinshasa, congo. *Phytomedicine*, *7*(1), 31–38. https://doi.org/10.1016/s0944-7113(00)80019-7

Trifković, K. T., Milašinović, N. Z., Djordjević, V. B., Krušić, M. T. K., Knežević-Jugović, Z. D., Nedović, V. A., & Bugarski, B. M. (2014). Chitosan microbeads for encapsulation of thyme (thymus serpyllum l.) polyphenols. *Carbohydrate Polymers*, *111*, 901–907. https://doi.org/10.1016/j.carbpol.2014.05.053

Tušek, A. J., Benković, M., Valinger, D., Jurina, T., Belščak-Cvitanović, A., & Kljusurić, J. G. (2018). Optimizing bioactive compounds extraction from different medicinal plants and prediction through nonlinear and linear models. *Industrial Crops and Products*, *126*, 449–458. https://doi.org/10.1016/j.indcrop.2018.10.040

Viuda-Martos, M., Gendy, A. E.-N. G. S. E., Sendra, E., Fernández-López, J., Razik, K. A. A. E., Omer, E. A., & Pérez-Alvarez, J. A. (2010). Chemical composition and antioxidant and anti-listeria activities of essential oils obtained from some egyptian plants. *Journal of Agricultural and Food Chemistry*, *58*(16), 9063–9070. https://doi.org/10.1021/jf101620c